

## REMARKS

Applicants thank Examiner Lankford for the courtesy of a telephonic interview on March 3, 2008, when possible claim revisions were discussed. Applicants have revised the claims in line with that discussion, and they request reconsideration of this application in view of the revisions and the these remarks.

### I. STATUS OF THE CLAIMS

The examiner previously refused entry of certain claim amendments, which applicants have resubmitted here. Claim 9 has been amended, and claims 41-44 have been added. Support for amendments to claim 9 can be found, for example, in paragraphs [0034] and [0040]. Support for the new claims can be found at least in paragraph [0021] and original claims 20-24. Upon entry of the amendments, claims 9, 11-12, and 27-44 will be pending in the application.

### II. REJECTIONS UNDER 35 U.S.C. § 112, ¶2

The examiner rejects claims 9, 11-12 and 27-40 for alleged indefiniteness. According to the rejection, the term “parent bacterial cells” is unclear. While applicants respectfully disagree, the amendment proposed by the examiner will not impact the scope of the pending claims. Accordingly, applicants have revised the claims in line with the examiner’s suggestion, which, they submit, should obviate the rejection.

### III. REJECTIONS UNDER 35 U.S.C. § 103

The examiner rejects claims 9-12 and 26-40 for alleged obviousness over Khatchatourians et al. Applicants traverse the rejection.

According to the examiner, Khatchatourians is cited for “teach[ing] the separation of minicells from normal, contaminating bacterial cells by inducing normal cells to filamentate followed by selective elimination of the filamentous bacteria.” Office Action dated May 15, 2007, pg. 3.

Khatchatourians actually taught (A) using low levels of penicillin to inhibit cell division but not longitudinal growth of *E. coli* cells and then (B) selectively eliminating

filamentous bacteria by sonic oscillation of whole cells, followed by centrifugation purification. *See* Khatchatourians, Discussion, ¶¶ 1-2 (Materials and Methods, “Preparation of minicells”); Declaration of Himanshu Brahmbhatt (“Brahmblatt Declaration”), ¶ 4. In proposing his method, Khatchatourians assumed that “sonic treatment disrupts whole cells” and “does not affect minicells” (page 293). This assumption proved to be false, however. *See* Brahmblatt Declaration, ¶ 6. In the decades following Khatchatourians’ 1973 publication, practitioners learned that sonication seriously damages minicells as well as bacterial cells. *Id.* In fact, as also evidenced by Henning *et al.*, *Proc. Nat’l Acad. Sci. USA* 76: 4360-64 (1979) (copy appended), sonication became the standard method of minicell *disruption* in the 1980’s and ‘90’s. *Id.*

Thus, Khatchatourians’ notion of preparing preparations of minicells is fundamentally flawed, as is the examiner’s rationale for rejection that is based on this reference. The skilled artisan, *circa* 2003, would have been well-aware of Khatchatourians’ error and, hence, would have dismissed the Khatchatourians methodology as illustrating how *not* to purify bacterial minicells. *See* Brahmblatt Declaration, ¶¶ 5, 7.

If anything, therefore, Khatchatourians teaches away from the presently claimed methodology and, certainly, cannot render applicants’ claims obvious within the meaning of Section 103. *Id.* For this reason alone, the pending Section 103 rejection should be withdrawn.

Furthermore, the examiner has acknowledged that Khatchatourians fails to teach the use of filtration to remove filamentous parent bacterial cells. In the absence of any suggestion on point, the examiner asserts that the skilled artisan, based on reasoning left unexplained on the present record, would have considered it obvious simply to replace Khatchatourians’ centrifugation purification step with “available filters.” Again, this assertion is flawed as a matter of fact.

The examiner has offered no evidence or reasoning why the person of ordinary skill would have deemed it straightforward, *a priori*, to make the “replacement” posited in the

Office Action. This contravenes the legal requirements of a sustainable Section 103 analysis, especially against the background of a rudimentary art in this regard, *circa* 2003.

With this last point in mind, applicants would emphasize that, even in theory, the use of filtration requires knowledge of the size and size uniformity of the particles to be purified. *See* Brahmlatt Declaration, ¶ 9. Yet neither of these prerequisites was known before applicants' invention. *Id.* Before applicants' discoveries, therefore, the skilled artisan would have had no factual basis for choosing among "available filters," in order to effect the exchange, posited by the examiner, for Khatchatourians' centrifugation step, and certainly would have lacked any principle or extant experience for expecting success from such an exchange. *See* Brahmlatt Declaration, ¶¶ 8-9.

In other words, the prior art evidences no "apparent reason to combine the ... elements," deemed known by the examiner, "in the fashion claimed" in this application (paraphrasing *Teleflex Inc. v. KSR Int'l Co.*, 82 USPQ2d 1385, 1389 (S. Ct. 2007)). Indeed, it was applicants' discovery that minicells from a diverse range Gram negative to Gram positive bacteria possess a uniform diameter, knowledge of which in turn informed applicants' inventive methodology. This uniformity was not presaged in the literature and was wholly unexpected. *See* Brahmlatt Declaration, ¶ 10. Applicants also were the first to determine that minicells have a diameter of approximately 0.4  $\mu\text{m}$  (400 nm). *Id.*, at ¶ 11.

By virtue of these discoveries, *inter alia*, applicants formulated the claimed methodology and demonstrated its use for separating minicells from filamentous parent bacterial cells. The result, a composition of minicells characterized by heretofore unattainable levels of purity, was likewise wholly unexpected in view of the contemporaneous literature. *See* Brahmlatt Declaration, ¶ 12.

Before the invention, "high-purity" minicell preparations contained 1 vegetative cell per  $10^6$  to  $10^7$  minicells. *See* Brahmlatt Declaration, ¶ 13. Since even a mouse therapeutic dose uses  $5 \times 10^8$  minicells, the previously available "high-purity" minicell compositions contained 50 to 500 live parent bacterial cells/dose, which would be lethal. *Id.* Thus, the inventive methodology, as presently claimed, satisfies a long-felt need, extant some 30 years,

for a process of obtaining minicell compositions containing fewer than about 1 contaminating parent bacterial cell per  $10^8$  minicells or less. *Id.* Indeed, applicants' discovery enabled for the first time the production of minicell compositions of pharmaceutical-grade purity, thereby clearing the way for minicells to advance from the research bench to pharmaceutical applications.

Accordingly, applicants submit that the examiner has not established a *prima facie* case of obviousness, and they request withdrawal of the rejection over Khatchatourians. They also request an early indication that this application is in allowable condition. Examiner Lankford is invited to contact the undersigned directly, should he feel that any issue requires further consideration.

The Commissioner is hereby authorized to charge any additional fees, which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, and to credit any overpayment to Deposit Account No. 19-0741. Should no proper payment accompany this response, then the Commissioner is authorized to charge the unpaid amount to the same deposit account. If any extension is needed for timely acceptance of submitted papers, then applicants hereby petition for such extensions under 37 C.F.R. §1.136 and authorize payment of the relevant fee(s) from the deposit account.

Respectfully submitted,

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